

Decentralization of clinical trials: opportunities, risks and development paths

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Abstract. The pandemic period represented, from many points of view, an opportunity for the updating of research processes, simplifying paths and highlighting the need to reflect on new ways of designing and organizing clinical trials. Starting from a literature analysis, a multidisciplinary working group composed of clinicians, patient representatives, university professors, researchers and experts in the field of health policy, ethics applied to health, digital health, logistics confronted with respect to the positive aspects, critical issues and risks that decentralization and digitalization can imply for the different target groups. The working group proposed feasibility guidelines of decentralized protocols for Italy, developing reflections that may be relevant also for other European countries.

Keywords. Decentralised clinical trials, Opportunities, Risks, European Health Data Space

1. Introduction

The pandemic period represented, from many points of view, an opportunity for the updating of research processes, simplifying paths and highlighting the need to reflect on new ways of designing or organizing trials that meet the needs of both companies and patients involved. From this point of view, Covid-19 has made it possible for European countries to see the importance of the digitalization of health information and at the same time the difficulties of accessing and sharing such data due to the complexity of rules, and in many cases the inadequacy and lack of interoperability of infrastructures and processes. The Decentralized Clinical Trials (DCT) represent an important turning point because they include the use of digital technologies, remote connections with the patient, dispensing and administration of therapies at home or in contexts other than the research centers and hospitals. This evolution is proving to have a significant impact on the different stakeholders involved. The study deepened the impact of the digitization and decentralization of clinical trials for patients directly involved, and more generally citizens, companies / sponsors, clinical centers (and related staff) involved in the trial, the national / regional health system, the logistics and delivery actors.

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Dealing with this issue is even more urgent considering the proposal made by the European Commission for the establishment of the European Health Data Space (EHDS), that should become one of the cornerstones of the European Health Union. The EHDS will provide a coherent, reliable, and efficient regulatory framework for the use of health data in research, innovation, policymaking and regulation, while ensuring full compliance with the EU's high data protection standards. The proposal presented by the European Commission is expected to enter into force in 2025.

2. Methods

The position paper is the result of a work carried out, with a participatory approach, by a multidisciplinary working group composed of clinicians representing some of the most impactful pathological areas (oncology, neurology, infectious diseases), patient representatives, university professors, researchers, and experts in the field of health policy, ethics applied to health, digital health, logistics².

Starting from a literature analysis of best practices at European level, the working group discussed of positive aspects, critical issues and risks that decentralization and digitalization can imply for the different target groups. Finally, they proposed feasibility guidelines of decentralized protocols for Italy, developing reflections that may be relevant also for other European countries.

3. Results

The pandemic has created new challenges for the conduct of clinical trials, which have required the search for alternative ways to continue clinical research. The adoption and development of new processes and new digital health solutions has been accelerated, making the need to integrate traditional medicine with digital medicine even more evident. At the international level, the DCT approach is already widely used in North America, while in Europe the development is made more complex by the greater concern with respect to the protection of privacy as well as the need to translate European indications into national regulations and guidelines.

DCTs refer to the introduction of technological components that allow remote data acquisition through different modes that rely on computer platforms and methods for data transmission and storage. Together with undeniable advantages in logistical terms, this entails great challenges from the point of view of equity (accessibility, age) and balancing with other rights, above all the right to privacy. The introduction of digitalization in clinical practice and in health systems goes far beyond the digitalization of health documents and the introduction of remote consultation. It has the potential to produce a real Copernican revolution on organizational, logistical, cultural as well as

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technological dimensions. In Italy, the innovation is mainly linked to the infrastructural transformation: a) collecting information methods and tools in a data federation logic, while protecting the privacy of individuals; b) exploitation of the huge number of health information produced for each access to health services and practices; c) standardization of health data collection systems on a common platform ensuring interoperability; d) moving from individual data to collective data; e) procedures capable of immediately reporting access to the emergency room, anomalies from wearable devices, or exceeding threshold of exam values, with notifications to researchers involved; f) usability of health information for final users.

The expected pros and Cons can be summed up as follows:

Table 1. Expected pros and Cons of the digitalization and decentralization of clinical trials.

Point of view	Pro	Cons/risks
Patients	Greater differentiation and inclusiveness of patient populations included in trials; facilitation of paediatric trials; increased clinical security; devices facilitate compliance and accuracy of procedures.	Privacy: data used also involve those of the patient's real life; Wearable devices may be uncomfortable to wear and visible (fear of stigma); Massive use of ICT could be a source of stress and lead to biases in the selection of patients. It changes doctor-patient relationship
Sponsors	Fewer barriers to recruitment and lower patient dropout rate; collect more data in less time and improved data quality; possible secondary (re)use of data; optimizing efficiency, time and costs of trials while maintaining all the characteristics of safety for patients and scientific validity.	Complexity of the approval process; uncertainties and regulatory issues; the use of electronic health records that comply with the conduct of a clinical trial is extremely limited: a cultural change is needed for all stakeholders, including companies.
Clinical centers and staff	Digital technology at the base of DCTs lightens some operational phases in charge of the centres; they offer enrolled patients health services and medical advice accessible anywhere and at any time; it facilitates doctor/patient communication by digital modalities; greater efficiency.	Centres often lack adequate connections and tools and with little interaction with their IT departments. The extensive use of IT devices requires the adoption of strong protection from accidental dissemination of sensitive data and from cyber-attacks. Medical staff are required to take on new responsibilities. Teams must be trained both on aspects related to technology (telemedicine, network access, patient privacy, etc.), and on specific communication skills.
The national/regional health system	DCT represents an opportunity for the healthcare system in terms of cost and efficiency. DCTs are a huge opportunity for health systems that will be able to invest in infrastructures and reorganizations. They can lead to greater competitiveness of the scientific research and opportunities for cross-fertilization with industrial sectors.	The costs of infrastructural transformation and of staff training.

4. Discussion

The increasing use of DCTs has an extremely important cost not only in terms of investments necessary for the digital transition but also in terms of ethical, managerial and governance risks. The expected *European Health Data Space* fits in this context promoting an easier access of patients to their health data as well as a single market for digital health services, regulated by strict privacy rules. The risk to be monitored is that the market and the logic of profit do not become the only real purpose of this new regulatory path. To this end, it will be necessary to monitor the procedures that will lead

to the definition of what is meant by secondary use of data in the various European countries, and to the definition of the rules of access to such data, as well as the composition of the Authority responsible for the access and use of health data, that should reflect the interests of the different stakeholders, including patients.

Finally, the fundamental question to be asked is that of who will bear the costs of the change, paying attention to the fact that the huge costs of such a change do not fall on citizens with a shift of resources at the expense of spending on care and assistance.

5. Conclusions

The debate highlighted that the emergency favored a significant progress in the direction of simplifying and accelerating the regulatory management of clinical trials, but in a context lacking legislation or guidelines. To seize this opportunity, there are several knots that must be untied. The Working Group suggests: from a **regulatory point of view**, to work on the development of regulations and guidelines, from an **institutional** point of view to strengthen the IT system of clinical centers; from an **ethical** point of view, to address key issues concerning patients, the community of citizens and public health. From an **operational** point of view, a new model of patient-centred clinical trials needs to be defined. From a **cultural** point of view, the new scenario can only start from the promotion of a new culture in digitization among patients, medical staff and all stakeholders involved in the process.

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